Cancer Incidence After Nasopharyngeal Radium Irradiation

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Background. From 1940 until 1970, nasopharyngeal radium irradiation was used to treat children and military personnel suffering from Eustachian tube failure attributable to local lymphoid hyperplasia.
Methods. We studied cancer incidence in a cohort of 4339 Dutch patients treated with nasopharyngeal radium irradiation, mostly in childhood, and 4104 frequency-matched nonexposed subjects. Average doses to the nasopharynx, pituitary gland, brain, and thyroid gland were 275, 10.9, 1.8, and 1.5 cGy, respectively. We assessed cancer incidence from cancer registry linkage (1989–1996), self-report including medical verification (1945–1988), and death certificates (1945–1996).
Results. During 18–50 years of follow-up, four thyroid malignancies (standardized incidence ratio [SIR] = 2.8; 95% confidence interval [CI] = 0.8–7.2) and five malignant brain tumors (SIR = 1.3; CI = 0.4–3.1) were observed. Increased risks were observed for malignancies of lymphoproliferative and hematopoietic origin (SIR = 1.9; CI = 1.2–2.8) and breast cancer (SIR = 1.5; CI = 1.1–2.1). Strong dose-response trends could not be demonstrated for any cancer outcome, although relative risk estimates were elevated in the highest-dose category for head and neck cancer and breast cancer.
Conclusions. These data provide little evidence for a high excess risk of cancer associated with nasopharyngeal radium irradiation treatment as applied in the Netherlands. Inconsistent findings across studies and public concern warrant the continuing follow-up of available cohorts.
(EPIDEMIOLOGY 2002;13:552–560)

Key words: cancer, radiation, head and neck.

Follow-up studies of cohorts of children treated for tinea capitis, hemangioma, and enlargement of thymus, adenoid, or tonsils in the decades before 1960 have demonstrated elevated risks for malignancies of the brain, thyroid, and salivary glands.[1–5] Treatments for these benign head and neck conditions typically involved external beam radiation (x-rays) with low to moderate radiation exposures to the thyroid gland (0.1–1.4 gray [Gy]) and brain (>1 Gy).

Forty years ago, nasopharyngeal radium irradiation (NRI) was used widely to ameliorate Eustachian tube dysfunction and to decrease hearing loss in children suffering from chronic otitis serosa or recurrent adenoid growth.[6] NRI was also used in World War II military personnel with aerotitis media.[7] NRI treatments consisted of insertion of a radium capsule through the nostrils to shrink accumulated lymphoid tissue in the nasopharynx. This typically produced low radiation doses to the thyroid gland (<0.05 Gy) and the brain (<0.2 Gy).[8] In the United States, 0.5 to 2.5 million children are thought to have been treated with NRI in the period 1946–1961.[9]

Prompted in part by public concern raised in the early 1990s,[10–12] cohort studies were undertaken to address the delayed health effects of NRI. Small excesses have been reported for head and neck cancer fatalities among 1214 NRI-treated World War II submariners[13] and for brain tumors among 904 U.S. children.[14,15] We studied a Dutch cohort of over 4000 exposed patients and observed no excess of head and neck cancer mortality in this group.[16] Here we report on cancer incidence, allowing for the evaluation of a greater number of cancer cases

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This study was supported by the National Cancer Institute (N01-CP-33013).

Submitted 22 August 2001; final version accepted 23 April 2002.

DOI: 10.1097/01.EDE.0000021464.28600.BE

and for the study of cancers, such as thyroid cancer, with a generally good prognosis.

Methods

Study Population

Building on a previously defined cohort,[17] we recruited an expanded cohort of patients who had been treated by ear, nose, and throat (ENT) physicians between 1945 and 1981 in the ENT departments of nine clinics in the Netherlands. We studied 5358 eligible patients ever treated with NRI and a frequency-matched (by clinic, sex, birth, and first treatment year) nonexposed group of 5265 subjects who had also been treated for ENT conditions but had never been exposed to NRI. Institutional review boards of all participating hospitals and research institutes approved the study protocol. Detailed descriptions of data collection, follow-up, and dosimetric methods have been reported elsewhere.[16]

Radiation Dosimetry

Radiotherapy characteristics were determined from the individual ENT treatment charts. In most clinics, one treatment course typically consisted of three or four 7- to 15-minute sessions, separated by intervals of 1 or 2 weeks. The treatments ranged from 3 to 74 milligram-hours (mgh; mg of radium multiplied by treatment duration in hours). Organ-specific doses were calculated based on simulations in age-appropriate, anthropomorphic phantoms, taking into account the distance from the radium applicator to the organ of interest.[8,16] Mean tissue doses to nasopharynx, pituitary gland, brain, and thyroid gland were 275, 10.9, 1.8, and 1.5 cGy, respectively, whereas mean tissue-absorbed doses to the total active bone marrow (ABM) and breast were only 0.4 and 0.1 cGy, respectively.[16] The average dose for head and neck ABM was 1.9 cGy (range 0.3–8.1 cGy).

Follow-Up

Cohort members were traced through 15 September 1997 at municipal resident registries and other relevant sources to determine vital status and address. In all, 92% were successfully traced.

Assessment of Cancer Incidence

Cancer incidence was assessed through record linkage with the Netherlands Cancer Registry (NCR) for the period 1989–1996, and through a health questionnaire survey coupled with medical verification of self-reported tumors for the period 1945–1988 (see below). For cohort members who had died, cause of death information was obtained from Statistics Netherlands and coded according to revisions of the International Classification of Diseases (ICD) applicable in the calendar period of death. For this study, all registered causes from earlier revisions were re-coded according to the ninth revision (ICD-9).[18] If a subject died of cancer but did not have a cancer diagnosis in the period 1989–1996, the cause and date of death were used as proxies for cancer incidence data.

Health Questionnaire Survey

In 1997, a questionnaire, a letter of introduction from an ENT-physician of the hospital where the subject was treated, and an informed consent form were mailed to each living subject in the cohort. Exposed and nonexposed subjects received identical letters. Consent was obtained for release of personal and medical data from participating ENT physicians, maintenance of the study database including personal identifiers for prospective follow-up, and record linkage with the Netherlands Cancer Registry.

We defined three response groups: (a) subjects who completed and returned the questionnaire and the consent form (participants), (b) others who responded that they did not want to participate (refusers) and (c) true nonresponders. Refusers were not contacted again. Four weeks after the first mailing, all nonresponders received a reminder letter with a questionnaire and a consent form. Both the original and the reminder letter stated explicitly that the consent form should be returned blank if the subject chose not to participate in the study. Eight weeks after the first mailing, nonresponders were contacted by telephone and were asked to complete the questionnaire with the interviewer over the phone. Of all cohort members alive as of 1997, 71% participated, 14% refused, and 14% were nonresponders.

The questionnaire addressed sociodemographic characteristics, diseases known or suspected to be related to radiation exposure in the head and neck area (cancer, thyroid disease, and reproductive failure), and possible confounders (occupation, smoking, alcohol consumption, exposure to various radiation sources, and female reproductive characteristics). We identified participants who had potentially been diagnosed with a malignancy by including items on cancer, tumors, and "growths," and on hospital admissions, biopsies, and radiotherapy. If the response to one or more of the latter items was affirmative, we sent a new letter asking for the name of the treating physician and for completion of a second consent form to allow release of medical data for study purposes. If consent was obtained, the physician was asked for a pathology report of the reported disorder, as well as for copies of relevant correspondence or medical chart notes.

In addition to the medically confirmed cancer cases, we included three self-reported but medically unconfirmed cases, in which the questionnaires contained unequivocal information on organ site and malignant

TABLE 1. Distribution of Subjects, Person-Years of Observation, and Cancer Cases by Exposure Status

	Exposed		Non-exposed	
	N	Person-Years	N	Person-Years
Eligible study cohort				
Alive, Responder	3,440	108,014	3,088	102,122
Alive, Nonresponder*	598	18,037	702	22,205
Deceased	301	7,188	314	7,780
Total	4,339	133,239	4,104	132,105
Cancer case status				
Alive	65		56	
Deceased	103		98	
Excluded from present analyses				
Emigrants	265		259	
Lost to follow-up	167		173	
Alive, but refused†	586		728	

* True nonresponders were retained in the eligible cohort because information on disease status was available through linkage with the Netherlands Cancer Registry.
† Subjects who replied that they did not want to participate.

nature of the disease. At re-contact, these subjects were either too ill to participate further or had died.

Linkage with the Netherlands Cancer Registry

The NCR provided data for the period 1989 to 1996 only, as the nationwide registry was not yet fully operational before 1989. Completeness has been estimated to be 96%.[19,20] The linkage is based on a unique code consisting of the first four letters of the last name, sex, and birth date.[21] Linkage results were coded according to both the International Classification of Oncology (ICD-O)[22] and the ICD-9.[18] Linkage was allowed for all living and deceased subjects, except for refusers.

Definition of Analytic Cohort

From the total cohort of 10,623 subjects, 340 (3%) were excluded owing to loss of follow-up, 524 (5%) owing to emigration, and 1,314 (12%) because they refused to participate in the survey. Two persons who died were excluded because their causes of death were unknown. The analytic cohort comprised 4339 exposed and 4104 nonexposed subjects (Table 1). All cancers, including multiple primaries, were included in the analyses, except for nonmelanoma skin cancers.

Calculation of Person-Years

Person-years were accumulated from the date of first radium treatment for exposed subjects or the date of first consultation with the ENT physician for nonexposed subjects until the date of first tumor diagnosis, date of death, or 15 September 1997, whichever came first. Among nonresponders, person-years were accumulated through 31 December 1996, *ie*, the last date covered by the NCR linkage. In a supplementary analysis, which included NCR-determined cases only, person-year calculation was restricted to the time window from 1 January 1989 through 31 December 1996.

Statistical Analysis

First, we compared observed numbers of cancers (O) in the exposed and unexposed groups with expected numbers (E), which were calculated by applying the person-year distribution in the cohort to sex-, age-, and calendar-period–specific reference data from the NCR.[23,24] As nationwide data were available only for the years from 1989 onwards, we used reference data from the oldest Dutch regional Cancer Registry (Comprehensive Cancer Center South, Eindhoven) for the period between 1973 and 1988,[25,26] and extrapolated the average of the 1973–1975 rates to earlier years.

We stratified the data by calendar period of follow-up (1940–1949, 1950–1959,. . ., 1990–1997), sex, attained age (0–4, 5–9, 10–19,. . ., 70–79, and ≥80 years), treatment level (nonexposed, <10, 10–19, 20–29, 30–39, and ≥40 mgh), age at treatment (0–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, and ≥50 years), and clinic. For each cell, the number of person-years and the observed number of cases were tallied, and the expected number of cases of specific cancers was calculated. We also calculated for each cell the person-year–weighted averages of attained age, age at treatment, and organ-specific radiation doses. Standardized incidence ratios (SIRs), defined as the O/E ratio, were then computed and 95% confidence intervals (CIs) were calculated using Poisson assumptions for the observed frequencies.[27,28]

We directly compared the relative risks (RRs) of cancer between NRI-exposed and unexposed groups by Poisson regression using the cell-specific expected frequencies as surrogates for person-years.[29] That is, for each cell, the observed frequency was assumed to correspond to a Poisson variable with a mean equal to the expected frequency of the population (E), treated as known, multiplied by a parametric function that depended on exposure or estimated radiation dose (D).

Thus, the model for comparing nonexposed subjects and NRI-exposed subjects was mean $(O) = \alpha E$ for nonexposed subjects and mean $(O) = \alpha E\ (1 + \beta)$ for NRI-exposed subjects, where α and β are unknown parameters, $RR = 1 + \beta$, and the excess RR (ERR) = β. For comparison specific to radiation dose, the linear model is mean $(O) = \alpha E\ (1 + \gamma D)$, where γD = the ERR at dose D and the unknown parameter γ = ERR per unit dose.

Our analyses included a variable indicating whether year of diagnosis was before or after 1989, to adjust for the elevated potential for case finding after 1989. Be-

TABLE 2. Population Characteristics of the Netherlands NRI Cohort by Exposure Status and Distribution of Potential Confounders Among Survey Participants Only

	Exposed		Nonexposed	
	N	%*	N	%
Eligible cohort				
Gender				
Male	2471	57	2324	57
Female	1868	43	1780	43
Age at first treatment (yrs)†				
0–4	917	21	1732	42
5–9	2255	52	1254	31
10–19	691	16	652	16
≥20	476	11	466	11
Follow-up (yrs)				
<20	427	10	388	10
20–29	1476	34	1363	33
30–39	1581	36	1458	36
≥40	855	20	895	22
Attained age (yrs)				
<30	633	15	667	16
30–39	1275	29	1255	31
40–49	1382	32	1178	29
50+	1049	25	1004	24
All questionnaire participants	(N = 3,440)		(N = 3,088)	
Highest level of education				
Low	844	25	754	24
Medium	1460	42	1343	44
High	1064	31	902	29
Unknown	72	2	89	3
Smoking status (packyears)				
Never	1368	40	1209	39
<10	829	24	797	26
10–29	851	25	696	23
≥30	253	7	229	7
Unknown	139	4	157	5
Alcohol consumption (glasses/day)‡				
none	696	20	653	21
<1	1168	34	1124	37
1–2	1081	31	819	27
≥3	362	11	352	11
Unknown	133	4	140	4
Female questionnaire participants only	(N = 1,579)		(N = 1,414)	
Age at menarche (yrs)				
<12	217	14	206	15
12–14	1100	70	958	68
≥15	235	15	229	16
Unknown	27	1	21	1
Number of children				
None	486	31	485	34
1–2	825	52	714	51
≥3	261	17	205	14
Unknown	7	<1	10	<1
Age at first birth (yrs)§				
<25	373	34	320	34
25–29	476	44	383	41
≥30	226	21	201	22
Unknown	18	2	25	3
Menopausal status				
Premenopausal	1018	64	910	64
Postmenopausal	308	20	286	20
Unknown	253	16	218	15

* Because of rounding, percentages do not always add up to 100%.
† Date of first treatment refers to first radium treatment session among exposed and to first consultation among control subjects.
‡ Refers to alcohol consumption during year preceding the 1997 questionnaire.
§ Percentage based on total number of parous women.

cause none of the RR estimates was substantially altered, these analyses are not presented here.

To evaluate risk of non-Hodgkin's lymphoma by dose region, we divided the body into five anatomically defined dose regions, ranging in dose from very high (nasopharynx and tonsils) to virtually zero (below diaphragm), as surrogates for dose at lymphoid tissues. Region-specific *E*'s and *O*/*E* ratios were calculated with non-Hodgkin's lymphoma reference rates by anatomic site from the Maastricht Cancer Registry (1986–1998).

Results

NRI-exposed and nonexposed subjects were similar with regard to gender, age, and follow-up time characteristics (Table 2). The majority of exposed subjects had their first radiation treatment before age ten, and were followed for 20–40 years. Most were between 30 and 59 years old at the end of follow-up. Relevant covariates for the analysis of cancer were generally equally distributed in exposed and nonexposed survey participants.

In the exposed group (Table 3), a total of 168 cancer cases was observed compared with 142 expected (SIR = 1.2). Fourteen malignancies in the head and neck area occurred (SIR = 1.3), including four thyroid malignancies (two papillary and two follicular tumors) (SIR = 2.8; CI = 0.8–7.2), two pharyngeal cancers (SIR = 2.0; CI = 0.0–7.2), and five brain cancers (ICD-9: 191) (SIR = 1.3; CI = 0.4–3.1). Three of the brain cancers among the exposed were astrocytoma and two were malignant but of unknown histology. When two fatal brain neoplasms of unspecified nature (ICD-9: 239.6)[16] were included in the analysis, the SIR was 1.9 (CI = 0.7–3.9).

We observed elevated risk of breast cancer in the exposed group based on 36 cases (SIR = 1.5; CI = 1.1–2.1), whereas the overall risk of female genital tract cancers was decreased, mainly attributable to a deficit of cervical cancer. Risk of malignancies of hematopoietic and lymphoproliferative origin was elevated among exposed subjects (SIR = 1.9; CI = 1.2–2.8), mainly attributable to excess risk of non-Hodgkin's lymphoma (SIR = 2.3; CI = 1.2–4.1). Elevated risks were observed for multiple myeloma (SIR = 3.1; CI = 0.9–8.0) and leukemia (SIR = 2.0; CI =

TABLE 3. Cancer Incidence in the Netherlands NRI Study, by Exposure Status

Tumor Site*	Exposed Group			Non-Exposed Group			Direct Comparison	
	O	SIR	95% CI	O	SIR	95% CI	RR	95% CI†
Head and neck area‡	14	1.3	0.7–2.2	11	1.1	0.6–2.0	1.2	0.6–2.8
Brain	5	1.3	0.4–3.1	6	1.7	0.6–3.7	0.8	0.2–2.9
Thyroid	4	2.8	0.8–7.2	1	0.7	0.02–4.1	3.8	0.5–76.0
Pharynx	2	2.0	0.02–7.2	0		0.0–4.0		
Oral cavity	1	0.5	0.01–2.9	2	1.1	0.01–4.1	0.7	0.03–7.2
Larynx	2	1.1	0.01–4.0	2	1.2	0.01–4.3	0.7	0.09–6.3
Lung	28	1.4	0.9–2.0	26	1.4	0.9–2.0	1.0	0.6–1.8
Digestive tract	32	1.2	0.9–1.8	34	1.4	0.9–1.9	0.9	0.6–1.5
Breast	36	1.5	1.1–2.1	24	1.0	0.6–1.5	1.6	0.9–2.7
Female genital tract	6	0.5	0.2–1.2	12	1.0	0.5–1.8	0.5	0.2–1.3
Cervix	1	0.2	0.00–1.0	6	1.1	0.4–2.4	0.2	0.02–1.2
Ovary	3	1.0	0.2–2.8	5	1.5	0.5–3.5	0.6	0.1–2.3
Uterus	1	0.5	0.01–2.7	1	0.4	0.01–2.3	0.8	0.03–21.3
Prostate	3	0.5	0.1–1.4	6	1.1	0.4–2.4	0.5	0.09–1.8
Hematopoietic and lymphoproliferative§	25	1.9	1.2–2.8	12	0.9	0.5–1.6	2.3	1.1–4.8
Non-Hodgkin's lymphoma	12	2.3	1.2–4.1	5	1.0	0.3–2.4	2.7	1.0–8.7
Hodgkin's disease	1	0.3	0.01–1.9	2	0.7	0.01–2.5	0.9	0.04–24.3
Multiple myeloma	4	3.1	0.9–8.0	0		0.0–3.0		
Leukemia¶	8	2.0	0.9–4.0	5	1.3	0.4–2.9	1.9	0.6–6.5
Unspecified	6	1.7	0.6–3.8	5	1.5	0.5–3.5	1.1	0.6–6.5
All sites combined‖	168	1.2	1.0–1.4	154	1.1	0.9–1.3	1.1	0.9–1.4

O = observed number of cases; E = expected number of cases; SIR = standardized incidence ratio (O/E).
* Multiple primaries included in analyses: among exposed (N = 8): one case each of cancer of the stomach, rectum, anus, pancreas, breast, eye, multiple myeloma, and chronic myeloid leukemia (third primary); among non-exposed (N = 5): one cancer each of the breast, colon, cervix, uterus, and acute myeloid leukemia.
† Relative risk obtained from Poisson Regression, adjusted for attained age and age at treatment.
‡ Defined as ICD-9[18] codes 140–149, 160, 161, 191, 193.
§ Defined as ICD-9[18] codes 200–208.
¶ Subtypes of leukemia (number of cases), among exposed: acute lymphoblastic (one), chronic lymphoblastic (one), acute myelocytic (one), chronic myelocytic (three), subacute myelocytic (one) and unspecified (one); among non-exposed: acute lymphoblastic (one), acute myelocytic (two), acute monocyte (one) and acute erythrocyte (one).
‖ Numbers do not add up as not all tumor sites are mentioned in table.

0.9–4.0). For other major cancer sites, no excesses were found (Table 3).

In the nonexposed group, the SIRs were all close to 1.0 (Table 3). Therefore, the direct comparison of the exposed to the nonexposed group, as RRs, essentially reflected the pattern of SIRs for the exposed group, although with much wider CIs. Results for cancer sites of interest were very similar when the analysis was restricted to cancers ascertained by NCR (1989–1996) only (Table 4).

There were no clear patterns of cancer risk by age at treatment, although for breast cancer, SIRs were elevated among women treated at age 5 to 9 years (SIR = 1.8; CI = 1.0–3.0) or age 10 to 19 years (SIR = 1.7; CI = 0.9–3.1) (data not shown). Analysis by time since initial treatment showed slightly elevated SIRs for total cancer more than 20 years after treatment. There was evidence of a time trend only for breast cancer (*P* for trend = 0.03), with the highest risk among women treated with radium more than 30 years earlier (SIR = 2.0; CI = 1.3–3.0).

Table 5 shows RRs by categories of appropriate tissue dose for malignancies of interest. Compared with the nonexposed group, RRs for cancers in the head and neck area rose with increasing dose up to 3.1 among those exposed to nasopharyngeal doses of more than 600 cGy (*P* for trend = 0.06). Modeled as a continuous dose, the ERR per Gy to the nasopharynx was 0.2 (CI= −0.006–0.8). Dose-related risk estimates for brain and thyroid cancer were statistically unstable attributable to small numbers.

Risk for breast cancer was elevated (RR = 2.6) among females in the highest-dose category (>0.2 cGy)

TABLE 4. Cancer Incidence in the Netherlands NRI Study, Defined by Cancer Registry Linkage (1989–1996)

Tumor Site*	Exposed Group			Non-Exposed Group		
	O	SIR	95% CI	O	SIR	95% CI
Head and neck area	4	0.8	0.2–2.0	3	0.6	0.1–1.9
Breast	23	1.8	1.2–2.7	8	0.7	0.3–1.3
Non-Hodgkin's lymphoma	7	2.7	1.1–5.6	3	1.3	0.3–3.7
All sites combined‡	72	1.0	0.8–1.3	71	1.1	0.9–1.4

O = observed number of cases; E = expected number of cases; SIR = standardized incidence ratio (O/E).
* Observed numbers include three second tumors among exposed *ie*, colon after rectal cancer, rectal after prostate cancer, and multiple myeloma after prostate cancer.
‡ Numbers do not add up as not all tumor sites are mentioned in table.

TABLE 5. Evaluation of Radiation Dose Effects for Selected Cancer Sites in the Netherlands NRI Cohort Study

Dose Category	Mean Dose (cGy)	E	O	RR*	95% CI	P† (trend)
Head and neck area§						
Non-exposed	0	10.0	11	1.0‡		
Low¶	139	3.7	2	0.5	0.1–1.9	
Medium	299	4.6	6	1.1	0.4–3.1	
High	613	2.4	6	3.1	1.0–8.6	0.06
Female breast						
Non-exposed	0	24.2	24	1.0‡		
Low‖	0.01	6.2	7	1.2	0.4–2.6	
Medium	0.11	13.3	19	1.5	0.8–2.8	
High	0.29	4.3	10	2.6	1.1–5.7	0.03
Non-Hodgkin's lymphoma						
Non-exposed	0	4.9	5	1.0‡		
Low**	0.18	2.2	6	4.4	1.2–17.2	
Medium	0.35	1.9	3	1.5	0.3–6.4	
High	0.77	1.1	3	3.4	0.7–14.9	0.14
Leukemia						
Non-exposed	0	4.0	5	1.0‡		
Low**	0.18	1.7	4	2.5	0.6–11.1	
Medium	0.35	1.5	3	1.6	0.3–7.1	
High	0.77	0.7	1	1.4	0.1–8.9	0.47

E = expected number of cancers; O = observed number of cancers.
* Relative risk and confidence intervals obtained from Poisson Regression model, adjusted for attained age and age at treatment.
† Test for trend = likelihood ratio test for adding continuous dose variable to null model.
‡ Reference category.
§ Defined as ICD-9[18] codes 140–149, 160, 161, 191, 193.
¶ Dose to nasopharyngeal tissues (as surrogate for radiation exposure in head and neck area).
‖ Breast dose.
** Total active bone marrow (ABM) dose; mean active bone marrow dose in head and neck area (cGy) by dose category: 1.17 (low), 2.35 (medium), and 4.19 (high).

(Table 5). The ERR/cGy was 4.8 (CI = 0.2–13.3). For the subset of women who provided questionnaire information on breast cancer risk factors, adjustment for the number of children, age at first birth (among parous women), age at menarche, or highest level of education attained did not alter the risk estimates (data not shown).

Estimated risks for non-Hodgkin's lymphoma were highest in the low (RR = 4.4) and the high (RR = 3.4) groups defined by total ABM dose, with little evidence of a dose-response trend (*P* for trend = 0.14). For leukemia, there was no dose-response observed using dose to total ABM (*P* for trend = 0.47) (Table 5), or dose to ABM in the head and neck area. All multiple myeloma cases received an ABM radiation dose in the medium (N = 1) or high dose (N = 3) categories.

When restricted to exposed subjects only, category-specific RRs for head and neck cancers (but not for leukemia and non-Hodgkin's lymphoma) showed a monotonic increase with increasing dose. For breast cancer, elevated risk was restricted to the high-dose group (Table 5).

Because NRI was used to treat lymphoid tissue hyperplasia, we also evaluated non-Hodgkin's lymphoma risk by local lymphoid tissue dose. Cases with known location (11 of 12) were grouped by primary site of first presentation and compared with expected numbers per anatomically defined dose region. Known sites in the head and neck area included the parotid gland (N = 1), base of tongue (N = 1), and the cervical lymph nodes (N = 2). SIRs were elevated for all dose regions, but confidence intervals were wide and overlapping. The SIR for non-Hodgkin's lymphoma in the head and neck area combined was 2.3 (CI = 0.6–5.9).

Discussion

Our study of cancer risk in a cohort of Dutch patients treated with NRI after World War II does not indicate highly elevated risks of cancer in general, or of tumors in the head and neck area in particular.

The thyroid gland is known to be extremely radiosensitive in children.[3] However, because survival is so high, thyroid cancer cannot be evaluated appropriately in mortality studies. The incidence analysis demonstrated a three-fold increased risk (based on four incident cases) at an average thyroid dose of only 1.5 cGy. In the Maryland NRI cohort, two thyroid cancers were seen among 914 NRI-exposed subjects (RR = 4.2; 95% CI = 0.4–46.6) with a median thyroid radiation dose of 9 cGy.[14] Although the small numbers prevent any definitive conclusions, the results suggest a possible effect.

In accordance with the evaluation of mortality in this cohort,[16] we found no more brain cancers than expected, compared with a 14.8-fold (95% CI = 0.8–286) elevated risk in the Maryland NRI cohort (based on three cases),[14] and a slightly elevated risk of head and neck cancers as a group among 1214 adult submariners treated with NRI 50 years earlier (RR = 1.5; 95% CI = 0.6–3.5).[13] Hazen *et al.*[30] observed no elevated risk of brain

cancer, based on only one case among 417 NRI-treated subjects during 14.6 years of follow-up. It should be noted that the estimated dose to the brain in the Maryland cohort was 15–40 cGy (Shore, 1982,[31] cited in Land, 1986[32]), compared with 0.3–8 cGy in our cohort. Elevated risk of intracranial tumors (malignant or benign brain tumors) was reported after x-ray therapy for benign head and neck conditions[1,33] at brain doses generally higher than in our cohort but partly overlapping with those of the Maryland cohort. We did not observe benign brain tumors, although two cases of undetermined type were identified from death certificates. We limited analysis to malignant brain tumors because the Netherlands Cancer Registry has not collected data on nonmalignant intracranial tumors. Although there is no evidence of elevated risk for brain tumors in the Netherlands' NRI-exposed population so far, mixed results hamper any definitive conclusion on NRI-associated brain tumor risk at present.

We observed an overall two-fold increased risk of hematopoietic and lymphoproliferative malignancies with no clear evidence of a dose-response. Other NRI cohorts[13,14,30] either found no elevated risk or did not report on leukemia, multiple myeloma, and lymphoma, so there is no convincing evidence of a causal association between NRI treatments and subsequent risk of leukemia and multiple myeloma. We found a 2.3-fold elevated risk of non-Hodgkin's lymphoma among exposed subjects but evidence of a dose-response relation based on ABM or lymphoid tissue doses was lacking. This was true even though the radiation dose to lymphoid tissues in close vicinity of the pharynx, such as the tonsils (averaging 21 cGy, ranging up to 130 cGy), was much higher than the total ABM dose. Similar results regarding risk of non-Hodgkin's lymphoma were obtained from an analysis of cancer mortality in this cohort;[16] however, seven out of 12 incident (exposed) cases represent subjects who died from non-Hodgkin's lymphoma.

Non-Hodgkin's lymphoma is usually considered not to be related to radiation.[34,35] Other risk factors for non-Hodgkin's lymphoma among NRI-treated subjects may play a role. Liaw *et al.* reported elevated risk of lymphoma after tonsillectomy; they speculated that this might be related to altered immune function after tonsillectomy (with or without adenoidectomy) in early childhood and simultaneous exposure to viruses associated with tonsillitis (such as the Epstein-Barr virus).[36] Elevated risk of non-Hodgkin's lymphoma is also seen among survivors of nasopharyngeal carcinoma (R. Curtis, oral communication, October 2001), a tumor with a known viral component that is also predominantly treated with radiotherapy.[37] Our finding of elevated risk of non-Hodgkin's lymphoma is remarkable if one considers the involvement of the lymphoproliferative system in the indication for NRI. However, this association may be attributable to chance alone, given the lack of confirmation from other radiation-exposed cohorts.

Recently, Yeh *et al.*[14] reported a 60% decrease in the risk of sex-hormone–related cancers in the Maryland cohort. They hypothesized a potential role of radiation-induced pituitary gland damage and decreased levels of circulating sex hormones. In our earlier mortality analysis of the Netherlands cohort,[16] we found a 1.7-fold (95% CI = 0.9–2.8) *increased* risk of death from breast cancer. The current analysis, based on nearly three times as many cases as the mortality analysis, continues to find an elevated (1.5-fold) risk of incident breast cancer. The two other NRI cohorts do not provide data on this issue. One cohort consists of males only,[13] and the other[30] reported too few breast cancer cases for meaningful evaluation, *ie*, zero exposed (E = 0.09) and three nonexposed (E = 0.98). Modan *et al.* did report slightly elevated risk of breast cancer in the Israeli tinea capitis study,[38] in which the average pituitary dose was intermediate between the Maryland study and our study. The breast doses were extremely low, comparable with our study. We found some evidence of a dose-response relation. However, the ERR of 4.8 per cGy to breast tissue would correspond to an ERR *per* Gy of over 400, under linearity assumptions, which is much higher than estimates from several independent studies reported by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (0.35 to 3.32 at 1 Gy).[34] The risk of female genital tract malignancies was modestly decreased, attributable to a deficit of cervical cancer, a malignancy known to have a strong viral rather than hormonal etiology.[39] The available data on women exposed to low-dose head and neck radiation as children do not allow for a unified conclusion with regard to breast cancer risk. In particular, it is difficult to disentangle any potential effect on cancer risk of radiation exposure to the pituitary gland (10–120 cGy) and breast tissue (<1 cGy) in these populations.

The results of this study should be viewed in light of some methodologic concerns. Despite the long follow-up and relatively large cohort size, case numbers are small and, consequently, risk estimates have wide confidence intervals. The possibility of chance findings should therefore be kept in mind for each of the estimates.

In the general population comparison (SIR analysis), selective refusal and incompleteness of case finding before 1989 are potential sources of bias. Among nonresponders, we have no information on case status before 1989. From the NCR linkage (1989–1996) we know that, in the exposed group, the SIR for total cancer among nonresponders was only slightly higher (6 observed cases; SIR = 0.7) compared with the SIR among participants (29 observed cases; SIR = 0.5). Among survey participants, medical file abstracts were retrieved

for 45% of all "cancer-suspect" questionnaire answers. Among all medically confirmed diagnoses, only 11% concerned a malignant tumor. We reported on the validity of self-report compared with the NCR linkage elsewhere.[40]

In the internal comparison (RR analysis), we assumed incompleteness in case finding to be nondifferential by exposure status. Death rates, tumor confirmation rates, and cancer rates (1989–1996) among nonresponders were indeed comparable for exposed and nonexposed subjects. As disease status of refusers and motives for refusal were unknown, we cannot exclude the possibility of differential refusal by disease status. On the other hand, our risk estimates based on cancer incidence compared well with the cancer mortality findings,[16] which are unaffected by selective participation.

We chose to include multiple primary cancers in the analyses because NCR reference data also include multiple primaries. Because second malignancies can be associated with treatment for a first cancer,[41] we repeated analyses including first primaries only. Although risk estimates were slightly reduced, main conclusions were by no means altered.

Strong features of the design include the availability of individual treatment records, a reasonably complete follow-up (92%) for both exposed and nonexposed subjects, the availability of an internal comparison group of nonexposed subjects, and the large size of the cohort compared with earlier studies.

In conclusion, these data provide little evidence for a high excess risk of cancer after NRI treatment as applied in the Netherlands. Inconsistent findings across studies, as well as public concern, warrant the continued follow-up of available cohorts.

Acknowledgments

We thank the Netherlands Cancer Registry, the Maastricht Cancer Registry, and the Eindhoven Cancer Registry for providing cancer incidence data; Leo Schouten and Hans Huveneers for assistance in the linkage procedure; Statistics Netherlands for providing causes of death; Willem Klokman for programming assistance; Susan Smith and Rita Weathers for help with dosimetry; John Boice and Donna Shriner for support and encouragement in the early phase of the study; Diane Fuchs for administrative assistance; and the following ENT-physicians and their staff for their cooperation: Ruud Havermans, Paul Mulkens, Gerard van de Meerakker, Tijo Bierman, Bert Annyas, Evert Rijntjes, Peter Olde Kalter, Harm ter Stege, and Gerard Bovenhorst.

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